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Original Research Article

Effectiveness of ursodeoxycholic acid therapy in intrahepatic cholestatsis of pregnancy

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ABSTRACT

Background: Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy specific disorder and commonly presents with maternal pruritus, abnormal liver function tests and adverse maternal -foetal outcomes. ICP lacks protocol-based therapy as etiology is multifactorial and is based on symptomatic treatment. The overall incidence of ICP is variable from 0.1 to 15.6% worldwide. The aim of this study is to assess the effectiveness of UDCA in ICP with regards to reduction in pruritus, normalizing LFTs and maternal-foetal outcomes.
Methods: This multicentric prospective study was performed from June 2017 to December 2019 in pregnant women with ICP attending the Antenatal clinic at INHS Patanjali, MH Dehradun, INHS Asvini, INHS Sandhani. In this study, 50 women with ICP. who satisfied the inclusion and exclusion criteria were started on UDCA therapy. The effectiveness of therapy was evaluated on the basis of normalization of LFT levels, reduction in pruritus, safe confinement, maternal-foetal outcomes and adverse effects if any
Results: The pregnant women with ICP on UDCA therapy showed marked improvement in pruritus, near normal LFT levels. After the UDCA therapy the frequency and intensity of pruritus was reduced in 50 (100%) of women. Safe confinement was achieved, with normal delivery in 45 (90%) women with no any major adverse effects and adverse maternal-foetal outcomes.
Conclusions: This study shows the effectiveness of URCA therapy in reducing the ICP associated pruritus, normalizing LFTs and safe confinement without any major adverse effects. UDCA therapy is an effective and safe option in ICP.

Keywords: Intrahepatic cholestasis, Pregnancy, Ursodeoxycholic acid

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a common pregnancy-specific disorder, most commonly occurring in the late second or third trimesters of pregnancy. ICP clinically presents with maternal pruritus (especially over palms and soles and at night) altered liver function tests (elevated serum transaminases).[1] The overall incidence of ICP is variable from 0.1 to 15.6% worldwide.[2,3] ICP has a multifactorial etio-pathogenesis related to sex hormone synthesis, environmental factors, and genetic predisposition.[4,5] CP is associated with adverse foetal outcomes like preterm delivery, neonatal respiratory distress syndrome, fetal distress, and sudden intrauterine fetal death along with increased incidence of postpartum hemorrhage.[6,7]

ICP is a high-risk pregnancy and the delivery should be timed properly, outweighing the risk of prematurity and ICP complications. Induction of labour is recommended in such women with ICP after 37 weeks of gestation.[7] The cesarean section rate is not increased by the early

induction of labor Glantz et al, reported an increased risk of spontaneous preterm labour, asphyxial events, meconium stained liquor.[8,9]

ICP lacks protocol-based therapy and treatments are focused on symptomatic relief. Cholestyramine, SAdenosyl-L-methionine (SAMe), and ursodeoxycholic acid have been used.[10-12] Studies have shown UDCA to be effective in reducing pruritus and normalising the liver function tests in ICP.[13]

The aim of this study is to assess the effectiveness of UDCA in ICP with regards to reduction in pruritus, normalizing LFTs and maternal-foetal outcomes.

METHODS

The prospective multicentric observational study was performed from June 2017 to December 2019 in pregnant women with ICP attending the antenatal clinic at INHS Patanjali, MH Dehradun, INHS Asvini, INHS Sandhani.

Inclusion and exclusion criteria of this study were

- The diagnosis of ICP was based maternal pruritus in pregnancy with other causes of cholestasis excluded.
- Abnormal liver function tests-Elevation of serum aminotransferases (>30 U/l).

In this study, 50 women with ICP who satisfied the inclusion and exclusion criteria were started on UDCA therapy. They were started on UDCA medication as per the standard protocol using 300 mg/twice a day.

A detailed history including maternal age, gravidity, parity, complications of earlier pregnancies, body mass index, and use of drugs, medical history and heredity of ICP was obtained. In subsequent follow-up visits the improvement in maternal pruritus, LFT levels side-effects of UDCA if any were also recorded along with foetal ultrasound reports.

Maternal and foetal outcomes

Gestational age at induction of labour, duration of labour and obstetrical managements, Apgar scores (1, 10 min), birth weight were noted in this study.

Statistical analysis

The statistical analysis of the data thus collected is done by observational method of data analysis and computed in results respectively.

RESULTS

The patient's characteristics as collected during the study period was analysed and tabulated as shown in Table 1.

Table 1: The patient characteristics.

Variable	Range	Mean
Age in years	20-30	26
Onset of pruritus (GA in weeks	26-34	32
ICP diagnosis at (weeks)	28-36	33
Parity	G1-multi	G1

The mean gestational age at the beginning of pruritus was 32 weeks in the entire group.

As shown in the Table 1, the onset of ICP was in the late second and third trimester of pregnancy.

The mean gestational age at the diagnosis was 33 weeks and predominantly seen in first order pregnant women (Primigravidas).

Response to therapy

The protocol-based therapy with UDCA was started for all the patients in this study and the dose of UDCA was 300 mg/ twice a day as supported by the recent studies. The findings are shown below in Table 2.

Table 2: Response to UDCA therapy.

Parameters	Improvement
Pruritus	50 (100%)
LFTs	48 (96%)
Side effects	Nil

All women (100%) in this study showed improvement in the pruritus during the subsequent Antenatal visits while on UDCA therapy. None of the patients showed any major adverse effects and intolerance to UDCA as shown in the Table 2. If this study.

Liver function tests

As shown in Table 2 lFTs begun to decrease after starting the medication.

On every visit to the antenatal clinic, LFTs were repeated, preferably on a weekly basis. There was a declining trend in the values of serum transaminases with near normal values in 48 (96%) of women and in 2 cases the LFTs remained static but just above the normal levels.

Table 3: The obstetrics outcome in the study group.

Outcomes	Number of cases
Normal delivery	45 (90%)
LSCS	5 (10%)
Gestational age at delivery	37-38 weeks
NICU admission	Nil

Maternal -foetal outcomes

The obstetrics outcomes in this study were followed closely and analysed as shown in Table 3.

Obstetric and neonatal characteristics are presented in Table 3.

All patients in this study group were induced at 37 completed weeks of gestation with standard induction protocol.

Mothers on UDCA delivered at the mean gestational age of 37 completed weeks.

A total 45 (90%) of women achieved successful normal delivery and in 5 cases LSCS was done in view of non-progress of labor (3), cephalopelvic disproportion (2) cases respectively.

No adverse outcomes like postpartum hemorrhage, respiratory distress syndrome, still birth was observed in the present study which adds to the strength of present study.

Thus, the timing of delivery should be proper to reduce the ICP associated stillbirths at the same time not increasing the risks of prematurity.

DISCUSSION

UDCA is a very effective drug in the therapy of ICP. Studies conducted by Diaferia et al, supported the use of UDCA at dose of 600 mg/day as in this study.[13]

Its use has been associated with lower frequency of fetal distress and reduced aminotransferase in all treated women with a significant reduction of pruritus. The prospective study of Palma et al, supports the close antenatal monitoring of pregnancies affected by ICP.[14]

In the present study also, UDCA was effective in reducing pruritus and improving liver function test results in patients with ICP.

In this study levels of aminotransferases begun to decrease after starting the UDCA therapy.

According to the latest Studies UDCA treatment should be recommended for women with ICP and elective delivery at 37 weeks in addition to monitoring fetal well-being can significantly reduce the stillbirth rate without increasing caesarean section rate.[15-17]

Mazzella et al, reported no adverse reactions of UDCA (1.5-2 g/d) and showed UDCA therapy.[18] Improves both biochemical and clinical parameters of cholestasis and is safe for the fetus.

UDCA was beneficial in ICP patients in terms of improving maternal pruritus, liver tests and also the final outcome of pregnancy. UDCA was also well tolerated and no adverse side effects were detected neither in mothers nor newborns followed up for 3 months after birth. Zapata et al, concluded that UDCA was well tolerated by pregnant women and no adverse effects were detected in his study comparable to the present study.[19]

In this study there were no preterm deliveries (< 37 weeks) and associated NICU admissions. The recent study of Puljic et al, demonstrated that delivery at 36 weeks' gestation reduced the perinatal mortality risk as compared with expectant management.[20] They concluded timing of delivery has to take into account both the reduction in stillbirth risk balanced with the morbidities associated with preterm delivery.

ICP increases the risk of respiratory distress syndrome in the new born. Chappell et al, also reported planned delivery not to increase caesarean section rate significantly in patients with ICP.[21] As shown by Zecca et al, there were no stillbirths in the present study.[22]

Newborns in all the improved maternal and foetal outcomes supports the increased awareness of the disease, experienced management and protocol-based therapy had a good Apgar score of > 7, 9 at 1 and 5 minutes respectively. Rioseco et al study suggests that induction of labour may reduce intrauterine fetal death compared with expectantly management and is thus beneficial.[22] The improved maternal and foetal outcomes supports the increased awareness of the disease, experienced management and protocol-based therapy.

CONCLUSION

UDCA protocol-based therapy reduces maternal liver function tests, is well tolerated by pregnant women and without any adverse maternal, fetal or neonatal side effects. UDCA is effective and safe in the treatment of pregnant women with ICP.

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